The Correlation Between Ketamine and Posttraumatic Stress Disorder in Burned Service Members

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Background: **Predisposing factors for posttraumatic stress disorder (PTSD) include experiencing a traumatic event, threat of injury or death, and untreated pain. Ketamine, an anesthetic, is used at low doses as part of a multimodal anesthetic regimen. However, since ketamine is associated with psychosomatic effects, there is a concern that ketamine may increase the risk of developing PTSD. This study investigated the prevalence of PTSD in Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) service members who were treated for burns in a military treatment center.**

Methods: **The PTSD Checklist-Military (PCL-M) is a 17-question screening tool for PTSD used by the military. A score of 44 or higher is a positive screen for PTSD. The charts of all OIF/OEF soldiers with burns who completed the PCL-M screening tool (2002–2007) were reviewed to determine the number of surgeries received, the anesthetic regime used, including amounts given, the total body surface area burned, and injury severity score. Morphine equivalent units were calculated using standard dosage conversion factors.**

Results: **The prevalence of PTSD in patients receiving ketamine during their operation(s) was compared with patients not receiving ketamine. Of the 25,000 soldiers injured in OIF/OEF, United States Army Institute of Surgical Research received 603 burned casualties, of which 241 completed the PCL-M. Of those, 147 soldiers underwent at least one operation. Among 119 patients who received ketamine during surgery and 28 who did not; the prevalence of PTSD was 27% (32 of 119) versus 46% (13 of 28), respectively ($p = 0.044$).**

Conclusions: **Contrary to expectations, patients receiving perioperative ketamine had a lower prevalence of PTSD than soldiers receiving no ketamine during their surgeries despite having larger burns, higher injury severity score, undergoing more operations, and spending more time in the ICU.**

Key Words: **Ketamine, PTSD, PCL-M.**

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Up to 17% of returning Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) noninjured veterans report cognitive and psychological symptoms consistent with posttraumatic stress disorder (PTSD); however, increased levels of direct combat exposure with minor wounds or injuries correlate with higher rates of PTSD.[1] This is in contrast to recent data suggesting that among returning OIF/OEF battle injured soldiers PTSD rates are similar to those in noninjured soldiers.[2] Recent literature also points to a link between untreated pain and PTSD.[3–6] Ketamine, a nonbarbiturate intravenous anesthetic regaining popularity especially within military medicine, is used at low doses as part of a multimodal approach for treating pain in burn patients at the United States Army Institute of Surgical Research (USAISR) Burn Center. However, since ketamine is associated with psychoactive effects (dissociative and psychotic states), there is concern that it may increase the likelihood of developing PTSD. This study investigates the prevalence of PTSD in OIF/OEF service members who were treated for burns in our military treatment center and also investigates the potential relationship of ketamine and PTSD prevalence.

PTSD is a psychological disorder characterized by recurrent flashbacks, nightmares, emotional disturbances, social withdrawal, and forgetfulness. It often arises after a traumatic experience in which the participant is threatened with harm or death. Predisposing factors for PTSD include experiencing a traumatic event, threat of injury or death, and threat to one's physical integrity, such as untreated pain.[7,8] The risk of PTSD increases if the participant is physically harmed. This life changing disorder has been reported to affect almost half of the burn patient population, with civilian burn centers reporting a range of 8% to 45%.[9–12]

METHODS

The PTSD Checklist-Military (PCL-M) is a screening tool for PTSD that is authorized for use by the US military. It consists of 17 questions rated on a scale of 1 to 5 so that a total score of 17 to 85 is possible. Initially, a score of 50 or greater was considered a positive screen for PTSD. However,

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reevaluation of data determined a score of 44 or higher yielded a diagnostic efficiency of 0.900.[13] The questions are designed to capture one of three distinct clusters of symptoms: reexperiencing, avoidance or numbing, or hyperarousal. The complete diagnostic criteria for PTSD are described in the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd (1980) and 4th (1994) editions.[7,8]

The study population was US military soldiers who had sustained thermal injuries during OIF/OEF deployments, and who were cared for at the USAISR Burn Center between 2002 and 2007. This study investigated the prevalence of PTSD in burn patients receiving ketamine during their operation(s) compared with those not receiving ketamine.

To examine the relationship between burn size and PTSD in 241 injured OIF/OEF patients who completed the PCL-M, data were sorted into two groups based on burn size using 20% total body surface area (TBSA) burns as the cutoff point (less than 20% TBSA and 20% or greater TBSA). This cutoff was chosen because 20% TBSA is the medically accepted minimal burn size that produces both the maximal response of inflammation and the maximal hyperbolic response.

Inclusion criteria for this study required that the patient have been screened for PTSD using the PCL-M from years 2002 through 2007. After IRB approval, charts were reviewed to determine percent TBSA, injury severity score (ISS), total number of surgeries at the USAISR Burn Unit and the anesthetic regimen used, including amounts given. Using a standard opioid conversion calculator, narcotic medications were converted to IV morphine equivalents. Statistical analysis included the Mann-Whitney test for nonparametric data sets, the Spearman correlation test to determine the relationship between PTSD and other factors, and ROC analysis.

RESULTS

Of approximately 25,000 soldiers injured in OIF/OEF, 603 were burn victims treated at the USAISR Burn Center. Two hundred forty-one of these burn patients completed the PCL-M, and 147 of those screened underwent at least one operation at the USAISR. Intraoperatively, 119 received ketamine, and 28 did not receive ketamine (Fig. 1). The increased morbidity of patients who received ketamine was evidenced by significantly higher %TBSA (21.43 vs. 10.22) and ISS (16.94 vs. 8.5) compared with those who did not receive ketamine. The ketamine group also had lengthier ICU stays (21.14 vs. 11.67 days) and more operative interventions (2.55 vs. 1.07) (Table 1).

Patients receiving ketamine demonstrated a lower prevalence of PTSD. Of those receiving ketamine, the prevalence of PTSD was 26.9% (32 of 119) versus 46.4% in those not receiving ketamine (13 of 28) ($p = 0.044$, Mann-Whitney test) (Table 2). Patients receiving ketamine on average had larger burns, more severe injuries, spent more time in the ICU, and had more surgical procedures. The demographics of the ketamine receiving population (ketamine) and the non-

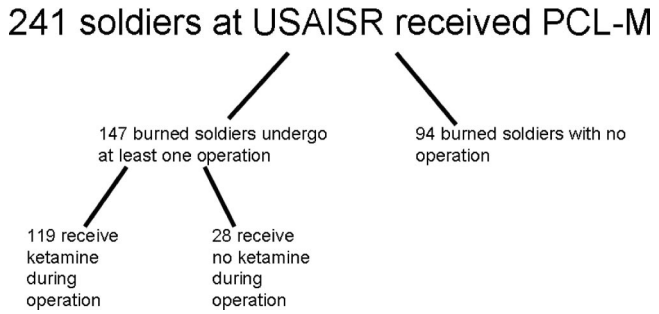

Fig. 1. *Patient population. Of the 25,000 soldiers injured in OIF/OEF, US Army Institute of Surgical Research (USAISR) received 603 burned casualties, of which 238 completed the PCL-M. Of those, 147 soldiers underwent at least one operation at the USAISR. During surgery, 119 received ketamine and 28 received no ketamine.*

Table 1 Patient Demographics

	Ketamine	No Ketamine
Gender (female/male)	4/114	4/24
Age	26 ± 6.0	25.1 ± 5.9
TBSA	21.43 ± 18.34*	10.22 ± 13.18*
ISS	16.94 ± 12.01*	8.5 ± 8.57*
ICU days	21.14 ± 36.76*	11.67 ± 38.8*
Number of operations	2.55 ± 2.52*	1.07 ± 0.26*
Morphine equivalent units per operation	76.1 ± 65.7	59 ± 58.1
Total morphine equivalent units in OR	219.7 ± 305.6*	66.8 ± 71.29*

* $p > 0.05$.

Table 2 Prevalence of PTSD

	Ketamine n = 119	No Ketamine n = 28
Number of patients with PTSD	32	13
Prevalence of PTSD (%)	26.89*	46.42*

* $p = 0.044$.

ketamine receiving group (no ketamine) are shown in Table 1. Based on the Mann-Whitney test for statistical significance on nonparametric data sets, all of the collected values of TBSA, ISS, ICU days, number of operations, and total morphine equivalent units during the surgical procedures were statistically significant. There were no statistical differences in the age of ketamine and nonketamine patients or in the amount of morphine per surgical procedure.

PTSD correlated with ketamine during surgical procedures (Table 3). Using SPSS correlation software to determine the Spearman coefficient, it was shown that PTSD correlated with ketamine, but did not correlate with morphine equivalent units during operations, size of the burn, severity of injury, days spent in ICU, or number of operations. The correlation coefficient is −0.166, meaning that ketamine usage was correlated with decreased PTSD. However, although PTSD correlated with ketamine, the correlation was weak

Table 3 PTSD Correlation Coefficients for Operative Patients

	PTSD
Ketamine	$r = -0.166^*$ ($p = 0.044$)
TBSA	$r = -0.085$ ($p = 0.308$)
ISS	$r = -0.092$ ($p = 0.266$)
ICU days	$r = 0.087$ ($p = 0.295$)
Morphine equivalents/operation	$r = -0.049$ ($p = 0.555$)
Total morphine equivalents in OR	$r = 0.046$ ($p = 0.584$)
Number of operations	$r = -0.045$ ($p = 0.588$)

$^*p < 0.05$.

with a receiver operating characteristic (ROC) curve of 0.569. Multiple factors other than ketamine will be required to reliably predict PTSD.

In this study population, burn size did not seem predictive of PTSD prevalence. Using the data from 241 soldiers admitted to the USAISR who completed the PCL-M, the prevalence of PTSD in the soldiers with burns less than 20% TBSA was 49 of 180 (27%), whereas soldiers with burns 20% or greater had a prevalence of PTSD of 17 of 61 (27.8%) (Table 4). This is despite the fact that 20% is the medically accepted standard size of burn that produces maximal response of inflammation and the maximal hyperbolic response.

However, to determine whether there is a percent TBSA burned that would be useful to predict PTSD development, the percent TBSA burned was plotted against the prevalence of PTSD (Fig. 2), the PTSD diagnosis (1 = yes, 0 = no) (data not shown), and the PCL-M score (data not shown). Best fit lines were determined and showed no significant change in slope across the spectrum of TBSA burn. This indicated that there was no standard sized burn that can be used to successfully predict PTSD development in this population.

Table 4 TBSA is Not Predictor of PTSD

	Burns Less Than 20% n = 180	Burns 20% or Greater n = 61
Number of patients with PTSD	49	17
Prevalence of PTSD (%)	27.2	27.87

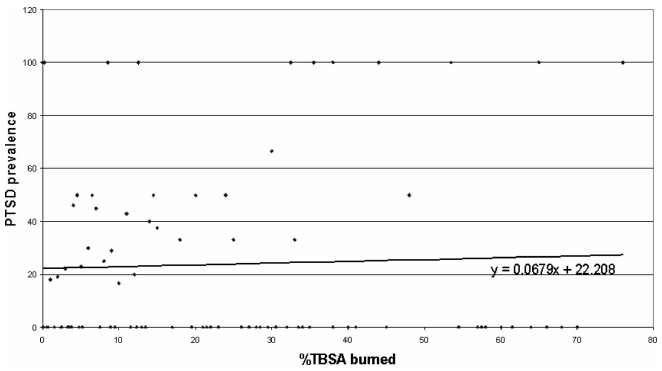

Fig. 2. *TBSA is not a good predictor of PTSD prevalence. Plot of percent TBSA burned vs. prevalence of PTSD in patients with that percent burn. The bestfit line is described with the equation* y = *0.0679*x + *22.208.*

DISCUSSION

Mechanisms to predict PTSD development are not well-developed. Initially, physical injury (burn size) was identified as a potential indicator of PTSD development. Recent studies have shown that PTSD does not correlate with burn size.[10,14] This study confirms that PTSD does not correlate with burn size in OIF/OEF soldiers and suggests that burn size is not a good marker for PTSD development in these patients.

The PCL-M is a 17-question screening tool for PTSD recommended for assessment of PTSD in military populations. A score of 44 or higher is considered a positive screen for PTSD and was used in this study.[13] The prevalence of PTSD in all 241 burned soldiers screened for PTSD (28%) is similar to the prevalence found in civilian burn populations (8%–45%).[9–12]

Ketamine is used as part of a multimodal anesthetic plan that usually includes an opioid component. Ketamine decreases the amount of opioid needed to effectively control pain. Ketamine is a multifunctional drug affecting multiple receptors including NMDA receptors, opioid receptors, and monoaminergic receptors.[15] It is used in total intravenous anesthesia where it functions as both an analgesic and an anesthetic depending on plasma concentration.[15] Ketamine acts as a profound analgesic at low doses by itself, as well as potentiating the effects of opioids. Ketamine is a non-competitive inhibitor of NMDA receptors that block Ca^{2+} channels.[16–18] With ketamine exposure, the NMDA receptor is not activated and does not initiate downstream signaling. Ketamine alters Ca^{2+},[16] cAMP,[19] protein kinase C,[20] and mitogen activated protein kinase[21] signaling.

Although ketamine is used in a multimodal anesthetic regime, it is associated with dissociative, psychotic, and psychodyslectic effects similar to those associated with PTSD. PTSD is characterized by over-stimulated brain activity. Contrary to concerns about additive effects upon brain activity and PTSD development, in this study the patients receiving ketamine during operative procedures had a lower prevalence of PTSD than soldiers receiving no ketamine during their surgeries despite having larger burns, more severe injuries based on higher ISS, undergoing more operations, and spending more time in the ICU. Soldiers receiving ketamine perioperatively also received more morphine equivalent units. However, the morphine equivalent units did not correlate with PSTD development. Our findings suggest that ketamine does not increase the prevalence of PTSD and may even decrease it. This allows ketamine to be added to the arsenal for effective pain relief.

The mediating effects of ketamine need to be examined further with known correlates of PTSD. Although traditional thinking has been to associate ketamine administration with increased incidence of PTSD, these results question that re-

lationship. In fact, it seems that ketamine may decrease the prevalence of PTSD in the combat burned patient. Potential explanations of this finding could include better pain management for patients receiving ketamine, neuronal protection by ketamine, and/or antagonism of the N-methyl-D-aspartate (NMDA) receptor by ketamine. Further research studies into the role of ketamine and individual anesthetic agents as well as various anesthetic techniques may help elucidate practical perioperative approaches in decreasing the prevalence of PTSD in the combat wounded as well as the civilian population who are at risk for this devastating disorder.

CONCLUSION

Perioperative low-dose ketamine use in burned soldiers undergoing surgery seems to decrease the prevalence of PTSD. The mechanism of this is unclear but could result from better pain control, neuronal protection by ketamine, and antagonism of the NMDA receptor. Further studies are necessary that determine the mechanisms of action and additional factors that will correlate with ketamine to predict PTSD outcome.

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DISCUSSION

Dr. Carl Andrew Castro (Walter Reed Army Medical Center, Washington, DC): Ketamine is a nonspecific, NMDA receptor antagonist that is widely used in low doses to control pain. Because ketamine is psychoactive and has been linked to increases in psychosomatic and psychotic symptoms, McGhee et al. predicted that burn patients who received ketamine would be at greater risk for screening positive for posttraumatic stress disorder (PTSD) than burn patients who did not receive ketamine. Contrary to expectations, only 26% of burn patients who received ketamine screened positive for PTSD, compared with 46% of burn patients who did not receive ketamine, despite the fact that those patients who received ketamine had larger burns, more severe injuries, spent more time in the intensive care unit and underwent more surgical procedures. McGhee et al. postulate that these findings might best be explained as a result of ketamine providing better pain control, neuronal protection, and antagonism of the NMDA receptor.

McGhee's findings remind me of one of my favorite movies, *Total Recall*, starring Arnold Swarzenegger. In this futuristic movie, we have developed the scientific and technical expertise to both erase someone's memory, as well as implant "false" memories. Let us consider for a moment the ability to erase memories. It is well established that antagonism of the NMDA receptor is also known to disrupt memory. Thus, an intriguing explanation for the findings reported by McGhee et al. is that ketamine reduces the prevalence of PTSD in burn patients by disrupting (or erasing) the memories of the unpleasant events associated with burn treatment and surgeries. It is also possible that ketamine might be disrupting or "erasing" the memories of the combat events or experiences directly. Indeed, research clinicians working with patients who have been diagnosed with PTSD have proposed using pharmacologic interventions to disrupt the memories of unpleasant events associated with PTSD. The idea would be

to reactivate the memory of the unpleasant combat experience in a clinical setting and then disrupt or "erase" that memory using a psychoactive drug that interferes with either memory consolidation, memory retrieval, or both. Such experiments have already been successfully conducted in studies with animals. Some investigators have even suggested giving pharmacologic agents as mental health prophylactics to Soldiers/Marines immediately after combat to inhibit the initial memory consolidation of unpleasant combat events that might lead to the development of PTSD.

Obviously much more research is needed to determine whether it is possible to specifically target unpleasant memories that can lead to debilitating illnesses such as PTSD and then "erase" these memories pharmacologically. One must also consider the ethical and moral issues surrounding "erasing" someone's memory, even if it is done to help them. Whether it is desirable or not to erase someone's memory, the findings of McGhee et al. provide some evidence, although admittedly only suggestive, that memory "erasing" just might be doable. But let's not forget one of the key lessons from the movie I mentioned earlier. Although erasing someone's memory was possible, it was also possible for there to be total recall at any time. Just like in real life, even in the future there are no simple solutions.

Dr. Laura McGhee (US Army Institute of Surgical Research, Fort Sam Houston, TX): Thank you very much, Dr. Castro, for your comments and insights. This was a retrospective study. We don't know the mechanism of ketamine action on PTSD prevalence. You mentioned possible mechanism of better pain control, neuronal protection, and antagonism of the NMDA receptor. Other possible mechanisms include interplay with other anesthetic medications and regimens: does the data suggest ketamine is protective or does it expose potential deleterious effects of other drugs such as opioids and volatile or inhalational agents. Future studies need to be done to identify the mechanism. The idea to reactivate the memory of combat in a clinical setting and disrupt it is a great point. This is indeed likely given conversations with many clinicians about patient reactions in the perioperative setting. The idea of giving pharmacologic agents as mental health prophylactics is good. Typically benzodiazepines are given but they are associated with a detrimental change in hemodynamic parameter that would be deleterious in the severely injured patients. Our data does not address the issue of memory erasing. Our data suggests that ketamine given during operative procedures does not increase PTSD prevalence and may even decrease it.